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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/825,177	04/16/2004	Axel Ullrich	034536-1468	8682

22428 7590 03/15/2006

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WASHINGTON, DC 20007

EXAMINER	
KAUFMAN, CLAIRE M	
ART UNIT	**PAPER NUMBER**
1646	

DATE MAILED: 03/15/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/825,177	ULLRICH ET AL.	
	Examiner	Art Unit	
	Claire M. Kaufman	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 April 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *7 and 8* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7 and 8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *16 April 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/16/04, 4/29/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The preliminary amendment filed 4/16/04 has been entered.

Inventorship

There is a discrepancy in the spelling of Inventor Nayler's name. In the Oath and Sequence Listing it appears as "Nayler", however, in the Application Data sheet it appears as "Naylor". Appropriate correction is required so that the data for this application is accurate.

Sequences

When a sequence is presented in a drawing, regardless of the format or the manner of presentation of that sequence in the drawing, the sequence must still be included in the Sequence Listing and a sequence identifier ("SEQ ID NO:X") must be used either in the drawing or in the Brief Description of the Drawings. See MPEP § 2422.02. In the instant application, a sequence identifier must be used for the sequences appearing in Figures 1-7.

According to 37 CFR 1.821(d) (MPEP § 2422), where the description or claims of a patent application discuss a sequence listing that is set forth in the "Sequence Listing" in accordance with paragraph (c) of this section, reference must be made to the sequence by use of the assigned identifier, in the text of the description or claims, even if the sequence is also embedded in the text of the description or claims of the patent application. Claim 8 recites amino acid sequence of Figures 1 and 2, but must instead refer to appropriate SEQ ID NO. Also, sequences appear in the application which are not referenced by SEQ ID NO, *e.g.*, p. 39, "HRDLAAR" in 5th line of EXAMPLE 1.

Appropriate correction is required.

Specification

The disclosure is objected to because of the following informalities: on p. 49, line 6, "30□C" should be --30°C--; it appears that "2gl" may be an error on p. 48, line 1.

Appropriate correction is required.

Title

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

The following title is suggested: "CLK2 ~~CLK~~ PROTEIN KINASES ~~AND RELATED PRODUCTS AND METHODS~~".

Abstract

Applicant is reminded of the proper content of an abstract of the disclosure:

A patent abstract is a concise statement of the technical disclosure of the patent and should include that which is new in the art to which the invention pertains. If the patent is of a basic nature, the entire technical disclosure may be new in the art, and the abstract should be directed to the entire disclosure. If the patent is in the nature of an improvement in an old apparatus, process, product, or composition, the abstract should include the technical disclosure of the improvement. In certain patents, particularly those for compounds and compositions, wherein the process for making and/or the use thereof are not obvious, the abstract should set forth a process for making and/or use thereof. If the new technical disclosure involves modifications or alternatives, the abstract should mention by way of example the preferred modification or alternative.

The abstract should not refer to purported merits or speculative applications of the invention and should not compare the invention with the prior art.

The instant abstract has speculative applications of the invention.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 7 and 8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 7 and 8 are indefinite because it is unclear what a "mCLK2 polypeptide" is. According to the specification on p. 11, second paragraph:

> The terms "mCLK2 ", "mCLK3", and "mCLK4 " refer to polypeptides that have amino acid sequences substantially similar to those set forth in Figure 1, Figure 2, Figure 4, or Figure 6. A sequence that is substantially similar will preferably have at least 95% identity, more preferably at least 96-97% identity,

> and most preferably 98-100% identity to the sequence set forth in Figure 1, Figure 2, Figure 4, or Figure 6. CLK protein kinase polypeptides preferably have protein kinase activity and fragments of the full length CLK protein kinase sequences having such activity may be identified using techniques well known in the art, such as sequence comparisons and assays such as those described in the examples herein. Other aspects of mCLK2, mCLK3, and mCLK4 nucleic acid sequences, amino acid sequences, functions and properties are further depicted in Nayler et al., 1997, Biochem J. 326: 693-700, hereby incorporated by reference herein in its entirety including all figures, tables, and drawings.

The specification does not provide a limiting definition of mCLK2. There is no minimum size and it may be similar to any of the sequences in Figure 1 not just the mCLK2 sequence. There is no limiting function, but only the preference that it have kinase activity. The metes and bounds of the claims are not clear.

Claim 8 requires a "unique fragment", which is defined in the specification (sentence bridging pages 22-23) as a "minimum stretch in amino acids in one CLK molecule that is different in sequence than any other portion of another protein kinase." One cannot determine if a fragment is "unique" by the definition of the specification because new protein kinases continue to be discovered and one cannot know if a fragment is actually "unique". One could, however, determine if a fragment is found in SEQ ID NO:20, 23 and 24, that is, if a fragment is present also in mCLK1, 3 or 4.

Claim 8 is also indefinite because it is drawn to a mCLK2 polypeptide, wherein said polypeptide is a fragment of a full-length sequence. The specification appears to distinguish between CLK polypeptides and fragments (see the middle of the above cited paragraph from page 11 of the specification). The claim is unclear. If the claim is drawn to a fragment, then it is suggested that "fragment" be added after the first occurrence of "polypeptide".

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 7 and 8 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a mCLK2 polypeptide comprising SEQ ID NO:21 and which is isolated, purified or enriched *in vitro*, does not reasonably provide enablement for a mCLK2 polypeptide comprising less than SEQ ID NO:21 or which is enriched *in vivo*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The specification does not provide a limiting definition of mCLK2 either in terms of structure of function (see rejection under 35 USC 112, second paragraph, above). The mCLK2 polypeptide of SEQ ID NO:21 is 499 amino acids long. It is structurally related to mCLK1, 3 and 4 of SEQ ID NO:20, 22 and 23, all of which are protein kinases. The "m" in front of CLK2 appears to designate that it is a murine protein (*e.g.*, see p. 4, last paragraph, of specification). When SEQ ID NO: 20-23 were individually expressed as GST fusions, all had catalytic activity. Referring to the ability to phosphorylate, it is stated (first paragraph of p. 45) that, "However, mCLK1 and mCLK4 displayed a dramatic difference in enzymatic activity versus mCLK2 and mCLK3." There was also a marked difference in catalytic activity of the two groups (first paragraph of p. 46). CLK proteins are also referred to as "LAMMER" proteins.

The claims are drawn to a "mCLK2 polypeptide", which appears to include a polypeptide 17 nucleotides long. There is no structural or functional limitation in claim7. Claim 8 has no functional limitation but does have a structural limitation requiring at least 17 contiguous amino acids from a full-length sequence in Figure 1 or Figure 2. The prior art taught human mCLK1, 2 and 3 (Hanes et al., #A40 reference) as well as a mouse CLK protein (Howell et al. and Ben-David et al., #A44 and #A14 references, respectively). SEQ ID NO:21 is 96% identical to human CLK2 and about 55% identical to human CLK1, CLK3, rat CLK3 (reference #A12), the prior art mouse CLK and a protein kinase from Drosophila melanogaster (Yun et al., #A95

reference). While the structures and functions of these proteins were known in the prior art, what sequence is required to make a CLK protein specifically murine or which particular amino acids are and are not required for catalytic activity was not known. While general features are presented (p. 36, first paragraph), these are not specific enough to allow the skilled artisan to predict which amino acids are sufficient and necessary for a mCLK2 protein without significant further research. Further, while the instant application shows a sequence comparison between mCLK1-4 polypeptides of SEQ ID NO:20-23, what amino acids make a polypeptide a "mCLK2" as opposed to a "mCLK1" is not known aside from the full-length sequence provided in the application. There is no guidance or examples of other sequences that can be a mCLK2 polypeptide. Further, it was shown that mutants with a lysine to arginine mutation(s) were catalytically inactive (top of p. 45). It has been shown by Hanes et al. (#A40) that there are alternative splicing forms of the human CLK proteins, adding more complexity to the issue of what a mCLK2 polypeptide is.

For the reasons discussed above, which include the breadth of the claims without functional limitation(s) and little or no structural limitation(s), the prior art's discussion of the different forms a CLK protein can have, the unpredictability of which amino acids are necessary to make a polypeptide a "mCLK2" polypeptide and the lack of guidance or examples relating to mCLK2 polypeptides with the exception of SEQ ID NO:21, it would require undue experimentation to make and use the invention commensurate in scope with the claims.

Additionally, the make an "enriched" mCLK2 polypeptide wherein the enrichment is *in vivo* would require undue experimentation. As "enriched" is defined in the specification (p. 21), it means the relative amount of mCLK2 in a cell has been significantly increased. This includes by transgenic manipulation or gene therapy-type of manipulation, neither of which the instant specification enables as a means of enriching mCLK2. These methods are extremely unpredictable. There is no showing in the specification that directed translation of a mCLK2 protein would be possible within a cell in an animal so that is was enriched. There is insufficient guidance to allow the skilled artisan to make the claimed product in this manner with a reasonable expectation of success and without undue experimentation.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 7 and 8 are rejected under 35 U.S.C. 102(b) as being anticipated by Hanes et al. (#A40) or Yun et al. (#A95).

Hanes et al. teach a CLK2 from human(Fig. 1) which is 96% identical to SEQ ID NO:21 of the instant application and comprises more than 17 contiguous amino acids of SEQ ID NO:21.

Yun et al. teach Drosophila darkener-of-apricot protein kinase which comprises amino acids 326-369 of SEQ ID NO:21 of the instant application.

Claim 7 is rejected under 35 U.S.C. 102(b) as being anticipated by Ben-David et al. (#A14).

Ben-David et al. teach a mouse CLK protein (Fig. 1).

Note that neither the claims nor the specification require a species of origin or a function. Only claim 8 has a structural limitation requiring 17 contiguous amino acids present in Figure 1 and 2. Sequence comparisons are found on the following pages.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Claire M. Kaufman, whose telephone number is (571) 272-0873. Dr. Kaufman can generally be reached Monday, Tuesday, Thursday and Friday from 9:30AM to 2:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback, can be reached at (571) 272-0961.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Official papers filed by fax should be directed to (571) 273-8300. NOTE: If applicant *does* submit a paper by fax, the original signed copy should be retained by the applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Claire M. Kaufman, Ph.D.

Patent Examiner, Art Unit 1646
March 7, 2006

SEQUENCE COMPARISONS TO SEQ ID NO:21=QY

Hanes, J.; von der Kammer, H.; Klaudiny, J.; Scheit, K.H.
J. Mol. Biol. 244, 665-672, 1994
protein kinase clk2, long splice form (EC 2.7.1.-) - human
C;Species: Homo sapiens (man)
C;Date: 15-Jul-1995 #sequence_revision 01-Sep-1995 #text_change 05-Oct-2004
C;Accession: S53637; T08825
A;Title: Characterization by cDNA cloning of two new human protein kinases. Evidence by sequence comparison of a new family of mammalian protein kinases.
A;Reference number: S53637; MUID:95082033; PMID:7990150
A;Accession: S53637
A;Molecule type: mRNA
A;Residues: 1-499
A;Cross-references: UNIPROT:P49760; UNIPARC:UPI0000127AD2; GB:L29218; NID:g632967; PIDN:AAA61482.1; PID:g632968
C;Comment: The short splice form of this protein (see PIR:S53638) lacks the protein kinase homology domain and associated catalytic sites.
C;Genetics:
A;Gene: clk2
C;Function:

A;Description: Phosphorylates Ser, Thr, and Tyr residues on proteins in the spliceosomal complex. May function as part of a regulatory system to control RNA splicing.
C;Superfamily: Protein kinase, CLK type; protein kinase homology
C;Keywords: alternative splicing; phosphotransferase
F;161-440/Domain: protein kinase homology

Query Match 96.1%; Score 2587; DB 2; Length 499;
Best Local Similarity 96.6%; Pred. No. 9e-117;
Matches 483; Conservative 7; Mismatches 8; Indels 2; Gaps 2;

```
Qy          1 MPHPRRYHSSERGSRGSYHEHYQSRKHKRRRSRSWSSSSDRTRRRRREDSYHVRSRSSYD 60
              |||||||||||||||||| |||:||||||||||||||||||||||||||||||||||||
Db          1 MPHPRRYHSSERGSRGSYREHYRSRKHKRRRSRSWSSSSDRTRRRRREDSYHVRSRSSYD 60

Qy         61 DHSSDRRLYDRRYCGSYRRNDYSRDRGEAYYDTDFRQSYEYHRENSSYRSQRSSRRKHRR 120
              | |||||:||||||||||||||||||:||||||:| |||| ||||||||||||||||||
Db         61 DRSSDRRVYDRRYCGSYRRNDYSRDRGDAYYDTDYRHSYEYQRENSSYRSQRSSRRKHRR 120

Qy        121 RRRRSRTFSRSSS-HSSRRAKSVEDDAEGHLIYHVGDWLQERYEIVSTLGEGTSGRVVQC 179
              |||||||||||||| ||||||||||||||||||||||||||||||||||||| ||||||
Db        121 RRRRSRTFSRSSSQHSSRRAKSVEDDAEGHLIYHVGDWLQERYEIVSTLGEGTFGRVVQC 180

Qy        180 VDHRRGGTRVALKIIKNVEKYKEAARLEINVLEKINEKDPDNKNLCVQMFDWFDYHGHMC 239
              ||||||| ||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        181 VDHRRGGARVALKIIKNVEKYKEAARLEINVLEKINEKDPDNKNLCVQMFDWFDYHGHMC 240

Qy        240 ISFELLGLSTFDFLKDNNYLPYPIHQVRHMAFQLCQAVKFLHDNKLTHTDLKPENILFVN 299
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        241 ISFELLGLSTFDFLKDNNYLPYPIHQVRHMAFQLCQAVKFLHDNKLTHTDLKPENILFVN 300

Qy        300 SDYELTYNLEKKRDERSVKSTAVRVVDFGSATFDHEHHSTIVSTRHYRAPEVILELGWSQ 359
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        301 SDYELTYNLEKKRDERSVKSTAVRVVDFGSATFDHEHHSTIVSTRHYRAPEVILELGWSQ 360

Qy        360 PCDVWSIGCIIFEYYVGFTLFQTHDNREHLAMMERILGPVPSRMIRKTRKQKYFYRGRLD 419
              |||||||||||||||||||||||||||||||||||:||||||||||||||||||||||
Db        361 PCDVWSIGCIIFEYYVGFTLFQTHDNREHLAMMERILGPIPSRMIRKTRKQKYFYRGRLD 420

Qy        420 WDENTSAGRYVRENCKPLRRYLTSEAEDHHQLFDLIENMLEYEPAKRLTLGEALQHPFFA 479
              |||||||||||||||||||||||||||:|||||||||:||||||||||||||||||||||
Db        421 WDENTSAGRYVRENCKPLRRYLTSEAEEHHQLFDLIESMLEYEPAKRLTLGEALQHPFFA 480

Qy        480 CLRTEPPNTKLWDSSRDISR 499
               || |||| ||||||||||
Db        481 RLRAEPPN-KLWDSSRDISR 499
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Yun, B.; Farkas, R.; Lee, K.; Rabinow, L.
Genes Dev. 8, 1160-1173, 1994

protein kinase Darkener-of-apricot (EC 2.7.1.-) - fruit fly (Drosophila melanogaster)
N;Alternate names: LAMMER protein kinase Doa
C;Species: Drosophila melanogaster
C;Date: 06-Jan-1995 #sequence_revision 06-Jan-1995 #text_change 05-Oct-2004
C;Accession: A54099; S44077
A;Title: The Doa locus encodes a member of a new protein kinase family and is essential for eye and embryonic development in Drosophila melanogaster.
A;Molecule type: mRNA
A;Residues: 1-517
A;Cross-references: UNIPROT:P49762; UNIPARC:UPI00001296A3; GB:X78715; NID:g472912; PIDN:CAA55367.1; PID:g472913
C;Genetics: A;Gene: FlyBase:Doa
A;Cross-references: FlyBase:FBgn0000480
C;Superfamily: Protein kinase, CLK type; protein kinase homology
C;Keywords: ATP; autophosphorylation; phosphotransferase; protein kinase
F;168-438/Domain: protein kinase homology

Query Match 8.8%; Score 44; DB 2; Length 517;
Best Local Similarity 100.0%; Pred. No. 1.7e-34;
Matches 44; Conservative 0; Mismatches 0; Indels 0; Gaps 0;

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Qy        326 DFGSATFDHEHHSTIVSTRHYRAPEVILELGWSQPCDVWSIGCI 369
              |||||||||||||||||||||||||||||||||||||||||||||
Db        333 DFGSATFDHEHHSTIVSTRHYRAPEVILELGWSQPCDVWSIGCI 376
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Ben-David, Y.; Letwin, K.; Tannock, L.; Bernstein, A.; Pawson, T. EMBO J. 10, 317-325, 1991
protein kinase STY (EC 2.7.1.-) - mouse
N;Alternate names: protein kinase clk
C;Species: Mus musculus (house mouse)
C;Date: 08-Nov-1991 #sequence_revision 08-Nov-1991 #text_change 05-Oct-2004
C;Accession: A39676; S13364
A;Title: A mammalian protein kinase with potential for serine/threonine and tyrosine phosphorylation is related to cell cycle regulators.
A;Reference number: S13364; MUID:91122038; PMID:1825055
A;Accession: S13364
A;Status: preliminary
A;Molecule type: mRNA
A;Residues: 1-378,'P',380-483
A;Cross-references: UNIPARC:UPI000002279F
A;Note: the sequence from Fig. 2 is inconsistent with that shown in Fig. 1 in having 448-Phe, 453-Val, and 456-Ile
C;Superfamily: Protein kinase, CLK type; protein kinase homology
C;Keywords: phosphotransferase; serine/threonine-specific protein kinase
F;158-429/Domain: protein kinase homology

Query Match 52.8%; Score 1422; DB 2; Length 483;
Best Local Similarity 55.7%; Pred. No. 3.1e-61;

```
  Matches  272;  Conservative   81;  Mismatches  121;  Indels   14;  Gaps
6;

Qy          1 MPHPRRYHSSERGSRGSYHEHYQSRKHKRRRSRSWSSSSDRTRRR----RREDSYHVRSR 56
              | | :| :  :   |   :  ::|    :|: || ||: :: | |    :  |||:: ||
Db          1 MRHSKRTYCPDWDERDWDYGTWRSSSSHKRKKRSHSSAREQKRCRYDHSKTTDSYYLESR 60

Qy         57 SSYDDHSSDRRLYDRRYCGSYRRNDY-SRDRGEAYYDTDFRQSYEYHRENSSYRSQRSS- 114
              |      :::  : |||   | ||||   : |  | :   |  |: |   || || |||
Db         61 S-----INEKAYHSRRYVDEY-RNDYMGYEPGHPYGEPGSR--YQMHSSKSSGRSGRSSY 112

Qy        115 RRKHRRRRRRSRTFSRSSSHSSRRAKSVEDDAEGHLIYHVGDWLQERYEIVSTLGEGTSG 174
              : |:|| |   |:  |   ||  :|::||||| |||||   || |  ||||| |||||  |
Db        113 KSKHRSRHHTSQHHSHGKSHRRKRSRSVEDDEEGHLICQSGDVLSARYEIVDTLGEGAFG 172

Qy        175 RVVQCVDHRRGGTRVALKIIKNVEKYKEAARLEINVLEKINEKDPDNKNLCVQMFDWFDY 234
              :||:|:||: || |||:||:|||::| |||: || ||| :|  || :   |||| :||::
Db        173 KVVECIDHKVGGRRVAVKIVKNVDRYCEAAQSEIQVLEHLNTTDPHSTFRCVQMLEWFEH 232

Qy        235 HGHMCISFELLGLSTFDFLKDNNYLPYPIHQVRHMAFQLCQAVKFLHDNKLTHTDLKPEN 294
               ||:|| ||||||||:||:|:|::||: :  :| ||:|:|::| ||| ||||||||||||
Db        233 RGHICIVFELLGLSTYDFIKENSFLPFRMDHIRKMAYQICKSVNFLHSNKLTHTDLKPEN 292

Qy        295 ILFVNSDYELTYNLEKKRDERSVKSTAVRVVDFGSATFDHEHHSTIVSTRHYRAPEVILE 354
              |||| |||   || : |||||:: :  ::|||||||:| |||||:||||||||||||||
Db        293 ILFVKSDYTEAYNPKMKRDERTIVNPDIKVVDFGSATYDDEHHSTLVSTRHYRAPEVILA 352

Qy        355 LGWSQPCDVWSIGCIIFEYYVGFTLFQTHDNREHLAMMERILGPVPSRMIRKTRKQKYFY 414
              |||||||||||||||: |||:|||:| |||:||||||||||||:|  ||:||||::||:
Db        353 LGWSQPCDVWSIGCILIEYYLGFTVFSTHDSREHLAMMERILGPLPKHMIQKTRKRRYFH 412

Qy        415 RGRLDWDENTSAGRYVRENCKPLRRYLTSEAEDHHQLFDLIENMLEYEPAKRLTLGEALQ 474
              ||||||::||||||   ||||: :: |:  :|  |||||  ||||:||||:|| |||:
Db        413 HDRLDWDEHSSAGRYVSRRCKPLKEFMLSQDAEHELLFDLIGKMLEYDPAKRITLKEALK 472

Qy        475 HPFFACLR 482
              ||||  |:
Db        473 HPFFYPLK 480
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